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Phase I trial of the MET inhibitor tepotinib in Japanese patients with solid tumors

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Abstract

Objectives: Tepotinib (MSC2156119J) is an oral, potent and highly selective small molecule mesenchymal-epithelial transition factor (MET) inhibitor for which the recommended Phase II dose of 500 mg once daily has been defined, based on the first-in-man trial conducted in the USA and Europe. We carried out a multicenter Phase I trial with a classic '3 + 3' design to determine the recommended Phase II dose in Japanese patients with solid tumors (NCT01832506).

Methods: Patients aged ≥20 years with advanced solid tumors (refractory to standard therapy or for whom no effective standard therapy was available) received tepotinib at 215, 300 or 500 mg once daily in a 21-day cycle. Occurrence of dose-limiting toxicities during cycle 1 was used to determine the maximum tolerated dose. Efficacy, safety and pharmacokinetics were also evaluated to support the dose assessment.

Results: Twelve patients were treated. Tepotinib was generally well tolerated with no observed dose-limiting toxicities; treatment-related adverse events were mainly grades 1–2. The tolerability profile of tepotinib was similar to that observed in non-Japanese populations. Pharmacokinetics in Japanese and Western patients was comparable. One patient with gastric cancer and one patient with urachal cancer had stable disease of ≥12 weeks in duration. The observed safety profile and pharmacokinetics are comparable with those in patients from the USA and Europe, and the recommended Phase II dose of tepotinib in Japanese patients was confirmed as 500 mg once daily.

Conclusions: These results, including initial signals of antitumor activity, support further development of tepotinib in Japanese patients with cancer.

Key words: clinical trials, molecular diagnosis, GI-stomach-Med

Introduction

Cancer is a leading cause of death in Japan, causing an estimated 379 900 deaths in 2018 (1), indicating the need for new, effective therapies. Development of new cancer therapies requires definition of an optimal dose in all target populations, between which dose variations are sometimes observed (2–4). Such variations can be mainly due to intrinsic differences, such as ethnicity (5). Phase I trials in different regions are therefore needed to assess safety, pharmacokinetics (PK) and pharmacodynamics (PD) to investigate and/or confirm the recommended therapeutic dose (4).

The growth of many solid tumors is driven by activated receptor tyrosine kinases (6), and kinase inhibitors can be effective in

controlling such growth. For example, inhibitors for the epidermal growth factor receptor (EGFR) and the vascular endothelial growth factor receptor (6) are well-established anticancer therapies. MET is a receptor tyrosine kinase that often shows abnormal activity in human cancers (7–9) and is associated with aggressive cancer phenotypes, metastatic dissemination and poor prognosis. Aberrant MET activation can arise through *MET* gene mutations (10), *MET* gene amplification (11) or overexpression of MET or its ligand (hepatocyte growth factor [HGF]) (12, 13). In turn, MET overactivity can drive tumorigenesis and confer resistance to other kinase inhibitor therapies through pathway cross talk, e.g. EGFR inhibitor resistance in non-small cell lung cancer (NSCLC) (9, 14). These actions of MET in tumor progression make it an important target for therapeutic intervention, particularly in tumors known to harbor MET alterations (9, 15–17).

Several MET inhibitors are currently in clinical development for patients with MET-driven tumors, with a focus on NSCLC (18). Tepotinib is a potent, highly selective, type Ib and orally administered MET inhibitor, with a 50% inhibitory concentration (IC_{50}) of 1.7 nM for MET (19), and screening against >400 kinases showed high selectivity of tepotinib for MET. The MET selectivity of tepotinib exceeds that of type Ia inhibitors such as crizotinib or type II inhibitors such as cabozantinib and is comparable with that of other type Ib inhibitors such as capmatinib and savolitinib (18). This selectivity minimizes off-target kinase inhibition at clinically relevant doses (7), maximizing the tolerability of tepotinib as a MET inhibitor. Tepotinib also has a large volume of distribution and high retention in tumor tissue, with sustained inhibition of MET and its downstream pathways, leading to inhibition of tumor cell proliferation and induction of apoptosis (7, 20).

In the first-in-man trial conducted outside of Japan (NCT01014936) (19), tepotinib monotherapy was generally well tolerated up to doses of 1400 mg once daily, and a maximum tolerated dose (MTD) could not be established. The optimal, biologically active dose was therefore defined by using PK and PD data from patients with advanced solid tumors in the first-in-man trial and through a translational modeling approach using KP-4 cell line xenografts in mice (19). As a result, tepotinib plasma concentrations of 390–823 ng/mL were established as being able to achieve ≥95% phospho-MET inhibition (19). Human population PK modeling indicated that this level of exposure should be achievable in >90% of patients by administering an oral once daily tepotinib dose of 500 mg, which has been defined as the recommended Phase II dose (RP2D) for further clinical trials (19).

We have conducted a Phase I study (NCT01832506) to determine whether use of this RP2D of tepotinib (500 mg once daily) is appropriate in Japanese patients with solid tumors, based on safety and PK data.

Patients and methods

Study design

This was a multicenter, open-label, non-randomized, single-agent, Phase I dose-escalation study in Japanese patients with advanced solid tumors. All patients provided written informed consent to participate in the study, which was conducted in accordance with the International Conference on Harmonisation guideline for Good Clinical Practice (GCP), the Declaration of Helsinki and the Japanese Ministerial Ordinance on GCP.

The study had a classic '3 + 3' dose-escalation design (21) with three tepotinib dose levels: 215 mg once daily, 300 mg once daily and 500 mg once daily administered in a 21-day cycle. The dose of 500 mg, used throughout the clinical development program of tepotinib, corresponds to 500 mg tepotinib hydrochloride hydrate (the active ingredient) and contains 450 mg tepotinib free base (the active moiety). To allow direct comparison with the first-in-man trial (NCT01014936), the same doses and capsule formulation as in the first-in-man trial were used. Patients were enrolled in sequential cohorts; three or six patients were scheduled to be enrolled to each of the first two cohorts (215 mg once daily and 300 mg once daily), and six patients were to be enrolled to the third cohort (500 mg once daily), if dose escalation (to 500 mg) proceeded. Treatment was continued until disease progression, withdrawal of consent or unacceptable toxicity occurred. Based on predefined criteria, there was an option to open a fourth dose level: 400 mg once daily or any other dose level between 500 mg and 300 mg, if 500 mg once daily was intolerable. To be evaluable, patients had to receive at least 80% of optimal dose during cycle 1, unless treatment was discontinued due to the occurrence of a dose-limiting toxicity (DLT).

Patients

Japanese patients aged ≥20 years with histologically or cytologically confirmed solid tumors refractory to standard therapy, or for which no effective standard therapy was available, were eligible. Other inclusion criteria included Eastern Cooperative Oncology Group performance status (ECOG PS) of 0/1 and life expectancy of ≥3 months. Patients were required to have an archived tumor sample or to undertake tumor biopsy.

Patients were excluded if they had: a history of central nervous system metastasis; human immunodeficiency virus infection; active hepatitis C or hepatitis B viral infection; histologically diagnosed liver fibrosis or liver cirrhosis; undergone major surgery within 6 weeks prior to Day 1 of cycle 1; hematological test abnormalities (hemoglobin <9.0 g/dL, neutrophil count $<1.0 \times 10^9$/L or platelet count $<100 \times 10^9$/L); renal impairment (serum creatinine >1.5 × upper limit of normal [ULN] and calculated creatinine clearance <60 mL/min); liver dysfunction (for patients without/with metastases: total bilirubin >1.5 × ULN, aspartate aminotransferase [AST] >2.5/>5 × ULN or alanine aminotransferase [ALT] >2.5/>5 × ULN); anticancer therapy within 4 weeks prior to Day 1 in cycle 1; extensive prior radiotherapy that irradiated more than 30% of bone marrow and/or any radiotherapy within 4 weeks before Day 1 in cycle 1; and therapy with any MET signaling pathway inhibitor.

Assessments

Safety. Treatment emergent adverse events (TEAEs) were assessed in accordance with Common Terminology Criteria for Adverse Events version 4.0 and reported from when informed consent was signed to the end of the post-treatment period. Upon completion of cycle 1 (i.e. the first 21 days of treatment) by the last subject at each dose level, data were presented to the safety monitoring committee for a decision on dose escalation.

In-line with the first-in-man trial (19), DLTs were defined as follows: grade 4 neutropenia for >7 days; grade ≥3 febrile neutropenia; grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding; grade ≥3 nausea despite adequate and optimal treatment; grade ≥3 non-hematological adverse events (AEs), specifically grade ≥3 liver AEs requiring a recovery period of >7 days to baseline level status or to grade ≤1 for patients without liver metastases or to grade ≤2 for patients with liver metastases or grade ≥3

lipase and/or amylase elevation with confirmation of pancreatitis (isolated grade ≥3 lipase and/or amylase elevation without clinical or radiological evidence of pancreatitis will not be classified as a DLT); or any AE of grade ≥2 not otherwise defined as a DLT that, due to prolonged recovery to grade 1 or baseline status, leads to a delay of tepotinib treatment for >21 days. The MTD was defined as the highest dose level at which DLT occurred during the first cycle in <2/6 patients. However, if ≥2/6 patients experienced DLTs at 500 mg once daily, tepotinib dose de-escalation to a dose such as 400 mg or any other optimal dose level between 300 and 500 mg once daily was predefined in the protocol.

Additional safety assessments included laboratory values, physical examination, vital signs, 12-lead electrocardiogram and ECOG PS.

Response. Baseline tumor status and response at the end of every second cycle were assessed by computed tomography or magnetic resonance imaging and judged by the investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (22).

Biomarkers. Up to 14 blood samples for biomarker analysis were collected during cycle 1 (Day 1 pre- and post-dose; Days 2, 3, 8 and 14 pre- and post-dose; and Days 15 and 17); cycle 2 (Days 1 and 14); cycles 3 and 4 (Day 1) and at end of treatment.

MET expression was assessed by immunohistochemistry (IHC) using CONFIRM anti-total MET (SP44) rabbit monoclonal primary antibody (Ventana Medical Systems). Tumor cells were scored as intensely, moderately or weakly positive or negative. Samples were defined as strongly positive (3+) if ≥50% of cells stained intensely; moderately positive (2+) if ≥50% of cells stained intensely or moderately but <50% stained intensely; weakly positive (1+) if ≥50% of cells stained better than weakly but <50% stained intensely or moderately and negative (0) if <50% of tumor cells showed any staining (23).

MET amplification status was assessed in relation to chromosome 7 centromere (*CEP7*) using dual-color dual-hapten brightfield *in situ* hybridization (DDISH) with the MET dinitrophenyl probe and Chr7 digoxigenin probe (Ventana Medical Systems). Sixty tumor cells were counted, and *MET* was considered amplified if the global average ratio of *MET*:*CEP7* was ≥2.0, and/or >10% of tumor cells had >15 *MET* copies and/or >10% of tumor cells had gene clusters (≥3 *MET* spots) in their nuclei (24).

High circulating levels of the MET ligand, HGF, have been associated with a poor prognosis in a variety of tumor types and as a potential indicator of MET/HGF pathway activation warrant investigation for possible predictive relevance for tepotinib (25). We therefore evaluated HGF levels in plasma samples, using an enzyme-linked immunosorbent assay.

Pharmacokinetics. Plasma samples for PK analyses of tepotinib were collected on Day 1 and Day 14 of cycle 1 at pre-dose and at 0.25, 0.5, 1, 2, 4, 8, 10 and 24 h post-dose. Further pre-dose samples were taken on Days 3, 8 and 17 of cycle 1 and on Day 1 of cycles 2–4. Samples were analyzed using a validated liquid chromatography/tandem mass spectrometry method. The methodology and frequency of PK sampling were in accordance with the previous first-in-man study (19). In brief, PK parameters including $C_{average}$ = average concentration at steady state, C_{max} = maximum plasma concentration and AUC_{0-t} = area under the plasma concentration versus time curve from time zero to the last sampling time (t) were evaluated.

Study objectives and analysis plan

The primary objective was to confirm the MTD and/or RP2D of tepotinib in Japanese patients with solid tumors, targeting the RP2D of 500 mg once daily established in non-Japanese patients. The primary endpoint was the number and proportion of patients experiencing a DLT.

Secondary objectives included (1) assessment of the safety profile of tepotinib; (2) evaluation of antitumor activity based on best overall response (BOR) (according to the objective response rate, clinical benefit rate and progression-free survival [PFS]) and (3) assessment of PK parameters.

Statistical analyses were performed using SAS version 9.3, except for non-compartmental computation of PK parameters, and descriptive statistical analyses of PK data, which were performed using Phoenix® WinNonlin® version 6.3.

Results

Patients

A total of 12 patients were treated with tepotinib, six of whom received tepotinib 500 mg. Demographics and baseline patient characteristics are shown in Table 1. The last study dose was administered on 17 September 2014.

Overall, patients completed a median of 1 cycle of therapy (range 1–17 cycles), with disease progression (n = 10) being the most common reason for treatment discontinuation (one patient withdrew consent, and one was withdrawn from the study in preparation for surgery). Median time on treatment was 1.35 months (range 0.82–11.76 months). For patients receiving tepotinib 500 mg, time on treatment was similar (median 1.36 weeks; range 0.85–11.76). Median time on treatment for patients receiving tepotinib 215 and 300 mg was 1.38 months (range 1.15–1.38) and 1.08 months (range 0.83–1.17), respectively.

Safety

No DLTs were observed at 215, 300 and 500 mg once daily. TEAEs and tepotinib-related TEAEs are summarized in Tables 2 and 3, respectively. Tepotinib-related TEAEs of any grade were reported in five (41.7%) patients. Those occurring in at least two patients were asymptomatic amylase/lipase increase, hypoalbuminemia, fatigue and dysgeusia. Grade ≥3 tepotinib-related TEAEs included grade 4 lipase increase in two patients in the 500 mg once daily group and grade 3 hyponatremia in one patient in the 500 mg once daily group. Neither of the patients with grade 4 increased lipase presented symptoms of pancreatitis or exhibited any signs of pancreatitis upon further radiological evaluation. No TEAEs resulted in permanent treatment discontinuation.

One patient in the 500 mg once daily group died due to disease progression. At the time of death, a serious AE of dyspnea was ongoing but was not considered related to treatment. No clinically relevant abnormalities were reported in vital signs and other safety observations.

Antitumor activity and biomarker analysis

Two patients (16.7%), both treated with tepotinib 500 mg once daily, had a BOR of stable disease (SD) ≥12 weeks. A male patient with a MET-expressing (IHC 2+) gastric cancer, who had received four prior lines of chemotherapy, achieved PFS of 4.6 months, and a male patient with urachal cancer (MET status was not evaluable) had PFS

Table 1. Patient demographics and baseline tumor characteristics

Characteristics	Tepotinib 215 mg once daily ($n = 3$)	Tepotinib 300 mg once daily ($n = 3$)	Tepotinib 500 mg once daily ($n = 6$)	Total ($n = 12$)
Median age, years (range)	60 (53–72)	62 (57–67)	69.5 (53–75)	64.5 (53–75)
Male/female, *n*	2/1	2/1	4/2	8/4
ECOG PS 0/1, *n*	3/0	2/1	4/2	9/3
Primary tumor site, *n*[a]				
Appendix	0	1	0	1
Anal cancer	0	0	1	1
Biliary tract	0	1	0	1
Breast	1	0	0	1
Esophagus	1	0	0	1
Lung	0	1	0	1
Rectum	0	0	1	1
Stomach	0	0	2	2
Thoracic esophagus	0	0	1	1
Urachus	0	0	1	1
Unknown	1	0	0	1
Prior lines of anticancer drug therapy, *n*				
0	0	0	1	1
1–2	0	0	2	2
≥3	3	3	3	9

[a]All tumors were adenocarcinoma and stage IV, apart from two squamous cell carcinomas and one tumor of unknown stage.
ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. TEAEs (any cause)

Patients with TEAE, *n* (%)	Tepotinib 215 mg once daily ($n = 3$)	Tepotinib 300 mg once daily ($n = 3$)	Tepotinib 500 mg once daily ($n = 6$)	Total ($n = 12$)
Any TEAE	2	3	6	11 (91.7)
Any treatment-related TEAE	1	1	3	5 (41.7)
Any serious TEAE	0	3	1	4 (33.3)
Any related serious TEAE	0	0	0	0
Any grade ≥3 TEAE	0	3	4	7 (58.3)
Any related grade ≥3 TEAE	0	0	3	3 (25.0)
TEAE leading to treatment discontinuation	0	0	0	0
TEAE leading to death[a]	0	0	1	1 (8.3)
Related TEAE leading to death	0	0	0	0
Related TEAE of special interest[b]	0	0	2	2 (16.7)

[a]Primary reason for death was disease progression.
[b]Defined as lipase or amylase elevation of grade ≥3.
TEAE, treatment emergent adverse event.

of 12.9 months, with tepotinib for metastatic disease after radiotherapy and surgery. Nine patients had a BOR of disease progression (75% overall). One patient was not evaluable. The median PFS was 1.38 (90% CI: 1.15–1.38) months.

MET expression by IHC and *MET* amplification by DDISH were assessed in the tumors of eight and seven patients, respectively (Table 4). Only one patient presented with IHC 2+ disease. *MET* amplification (gene clusters in >10% of tumor cells) was found only in one female patient with rectal cancer who had a BOR of progressive disease. Small patient numbers precluded statistical analysis of the relationship between *MET* abnormalities and response to treatment.

Median baseline HGF levels were 1602 pg/mL (range 1093–5768 pg/mL). HGF levels tended to increase slightly during tepotinib treatment. Notably, the patient with urachal cancer, who had PFS of 12.9 months, also had lower and more stable plasma HGF levels before and during tepotinib treatment (baseline 1176 pg/mL; end of treatment 1176 pg/mL). Other patients with similarly low baseline plasma HGF levels had a BOR of disease progression. In a patient with MET negative lung adenocarcinoma, HGF plasma

Table 3. Tepotinib-related TEAEs

TEAE, *n* (%)	Tepotinib 215 mg once daily (*n* = 3)	Tepotinib 300 mg once daily (*n* = 3)	Tepotinib 500 mg once daily (*n* = 6)	Total (*n* = 12)
Any grade				
Amylase increase	0	0	2	2 (16.7)
Lipase increase	0	0	2	2 (16.7)
Serum creatinine increase	0	0	1	1 (8.3)
Hypoalbuminemia	0	0	2	2 (16.7)
Decreased appetite	1	0	0	1 (8.3)
Hyponatremia	0	0	1	1 (8.3)
Nausea	0	0	1	1 (8.3)
Stomatitis	0	0	1	1 (8.3)
Vomiting	0	0	1	1 (8.3)
Fatigue	1	1	0	2 (16.7)
Dysgeusia	1	0	1	2 (16.7)
Acneiform dermatitis	0	0	1	1 (8.3)
Grade 3/4				
Lipase increase (grade 4)	0	0	2	2 (16.7)
Hyponatremia (grade 3)	0	0	1	1 (8.3)

Table 4. Tumor MET status

	Tepotinib 215 mg once daily (*n* = 3)	Tepotinib 300 mg once daily (*n* = 3)	Tepotinib 500 mg once daily (*n* = 6)	Total (*n* = 12)
Expression on IHC				
0	1	0	0	1 (8.3)
1+	2	2	2	6 (50.0)
2+	0	0	1	1 (8.3)
3+	0	0	0	0 (0.0)
Not available	0	1	3	4 (33.3)
Amplification status				
Amplified	0	0	1	1 (8.3)
Not amplified	2	2	2	6 (50.0)
Missing	1	1	3	5 (41.7)

IHC, immunohistochemistry.

concentration at baseline was exceptionally high (5768 pg/mL), but decreased significantly after the first tepotinib dose (10 h post-dose; 1278 pg/mL) before subsequently increasing (end of treatment; 2249 pg/mL). This patient had a BOR of disease progression.

Pharmacokinetics

Tepotinib exposure (C_{max}, AUC_{0-t}) after the first and multiple oral doses of tepotinib increased with dose in a less than dose proportional manner, as shown in Table 5. Drug accumulation over 14 days was noted in all but one patient, with mean C_{max} increasing from 2.0 ng/mL to 3.3 mg/mL and mean AUC_{0-t} from 2.5 to 4.0 h*ng/mL. Tepotinib trough concentrations remained stable for individual patients between cycles 1 and 4. Tepotinib exposure (C_{max}, AUC_{0-t}) in Japanese patients was similar to that of Western patients receiving the same doses in the first-in-man study.

The AUC_{0-t} on Day 14 for patients receiving tepotinib at 500 mg once daily ranged from 18 045 to 26 969 h*ng/mL, with average steady-state concentrations from 760.3 to 1126.8 ng/mL. Tepotinib exposure in all patients therefore exceeded the concentration range of 390–823 ng/mL that was defined to result in ≥90% target inhibition of the MET receptor (19).

Discussion

The approved dose of a drug can sometimes differ between countries due to population variability in terms of efficacy, toxicity and PK (4), as well as differences in the respective regulatory approval pathways (5). Therefore, it is essential to establish the optimal dose and regimen for new agents in different ethnicities and regions to ensure that efficacy and safety can be optimized.

We evaluated whether the dose established as the RP2D of tepotinib, based on modeling of data from the first-in-man trial conducted in non-Japanese patients (500 mg once daily (19)), was also appropriate for use in Japanese patients with advanced solid tumors. Based on the results of the trial reported here, the tolerability and safety profile and PK of tepotinib in Japanese patients are similar to those in Western patients. No DLTs were observed in Japanese patients in this trial. In addition, all Japanese patients who received tepotinib 500 mg once daily showed $C_{average}$ of >700 ng/mL at steady state and, thus, achieved tepotinib concentrations within the range defined to reduce tumor growth via inhibition of MET (19). Therefore, the RP2D of 500 mg given orally once daily was confirmed as appropriate for Japanese patients. Additional Phase Ib/II studies in Europe, USA, China, Taiwan, Singapore and South Korea also have confirmed the RP2D and shown that tepotinib is

Table 5. PK data at days 1 and 14

	Tepotinib 215 mg once daily	Tepotinib 300 mg once daily	Tepotinib 500 mg once daily
Day 1	($n = 3$)	($n = 3$)	($n = 6$)
C_{max} (ng/mL)	244.4 (29.9%)	301.3 (42.6%)	442.4 (27.5%)
	[193.0–339.0]	[188.0–385.0]	[305.0–650.0]
T_{max} (h)	8.0 [7.9–8.0]	8.0 [8.0–10.0]	10.0 [4.0–23.9]
AUC_{0-24h} (h*ng/mL)	4060.8 (30.7%)	5412.7 (45.0%)	8235.0 (30.9%)
	[3145.0–5652.0]	[3321.0–7443.0]	[5922.0–12 136.0]
T_{lag} (h)	1.95 [1.95–1.97]	0.97 [0.97–2.00]	0.99 [0.47–1.98]
Day 14	($n = 3$)	($n = 3$)	($n = 5$)
C_{max} (ng/mL)	807.5 (11.5%)	610.1 (84.4%)	996.8 (17.5%)
	[708.0–875.0]	[354.0–1410.0]	[801.0–1260.0]
T_{max} (h)	8.0 [8.0–8.0]	9.9 [2.0–10.2]	4.1 [3.9–9.9]
AUC_{0-t} (h*ng/mL)	16 088.6 (12.2%)	13 313.4 (82.5%)	21 509.0 (16.7%)
	[14 321.0–18 256.0]	[7891.0–30 291.0]	[18 045.0–26 969.0]
$C_{average}$ (ng/mL)	671.8 (11.9%)	554.6 (82.7%)	899.3 (16.4%)
	[599.6–760.1]	[328.1–1263.0]	[760.3–1126.8]
$CL_{SS/f}$ (L/h)	13.4 (12.2%)	22.5 (82.5%)	23.2 (16.7%)
	[11.8–15.0]	[9.9–38.0]	[18.5–27.7]

For $C_{max/average}$, AUC and $CL_{SS/f}$ values are geometric mean, (CV), [range] and for T_{max} and T_{lag} values are median, [range].
AUC_{0-24h}, area under the plasma concentration versus time curve from time zero (dose given) to the last sampling time (24 h) within one dosing interval; $C_{average}$, average concentration at steady state; $CL_{SS/f}$, apparent total body clearance of drug at steady state; C_{max}, maximum plasma concentration; h, hours; CV, coefficient of variation; PK, pharmacokinetics; T_{lag}, time prior to the first measurable (non-zero) concentration and T_{max}, time taken to reach maximum plasma concentration.

generally well tolerated in specific patient populations, such as those with hepatocellular carcinoma and NSCLC (26–29).

The majority of AEs in this trial were of grades 1–2. Grades 3–4 tepotinib-related TEAEs included edema, fatigue and asymptomatic increases in serum levels of AST, ALT and lipase. The treatment-related grade 3–4 events that occurred in this trial are similar in nature and incidence to those observed in completed and ongoing trials of tepotinib (19, 26–29). Amylase and lipase increases are considered as class effects because they have been observed in trials of other selective MET inhibitors, such as capmatinib and savolitinib (30–32), as well as in other trials of tepotinib (19, 26–29).

Based on the setbacks experienced in previous clinical development programs with other MET inhibitors, it is now commonly understood that strict selection of the patient population based on relevant MET alterations is of utmost importance (14, 16, 17). In this trial, however, assessment of the antitumor activity of tepotinib was only a secondary objective, and tumor MET status was not an entry criterion. MET overexpression (IHC 2+) and *MET* amplification were found in one patient each. Therefore, no conclusions regarding the association between MET status and response can be drawn from this trial. Nevertheless, a signal for antitumor activity was observed, with a BOR of SD for ≥12 weeks seen in 2 out of 12 patients. One of these patients had a MET overexpressing gastric tumor.

Since the conduct of the present study, *MET* exon 14 skipping has emerged as a promising biomarker for prediction of response to MET inhibition in patients with advanced NSCLC harboring this alteration in studies that have included Japanese patients (18). Recently, the Phase II VISION trial demonstrated durable clinical response to tepotinib in NSCLC harboring *MET* exon 14 skipping, with consistent efficacy in the subgroup of patients from Japan (33). Tepotinib was approved for use in advanced NSCLC with *MET* exon 14 skipping by the Japanese Ministry of Health, Labour and Welfare in March 2020 based on results from the VISION study and is the first MET inhibitor approved in Japan. Capmatinib has also shown antitumor activity in patients with NSCLC harboring *MET* exon 14 skipping in the Phase II GEOMETRY mono-1 trial (34), with similar activity observed in Japanese patients (35). Savolitinib is also currently being investigated in Chinese patients with *MET* exon 14 skipping NSCLC, and preliminary results have shown encouraging activity (36). While savolitinib is not currently being investigated in Japanese patients with *MET* exon 14 skipping, the ongoing Phase 1b TATTON study does include a Japanese cohort of patients with advanced solid tumors in order to establish dosing (37). Finally, crizotinib has demonstrated efficacy in *MET* exon 14 skipping NSCLC in a Phase II trial (PROFILE 1001) (38). Although data for the Japanese patients enrolled in this trial have not been presented separately to our knowledge, further evidence is expected from an ongoing Japanese study (Co-MET) (39).

We also analyzed plasma HGF levels to make a preliminary assessment of whether these might serve as a predictive marker for response to tepotinib. This analysis was inconclusive because only a small number of patients were enrolled and the limited response data precluded meaningful correlative analyses. The observation, that the patient with baseline HGF levels at the lower end of the observed range (which remained stable during treatment) went on to experience the longest PFS (12.9 months), is difficult to interpret as other patients with similarly low levels at baseline had a BOR of progressive disease and shorter PFS. Notably, the patient with the most significant decrease in HGF levels during treatment did not respond clinically. Although high baseline serum HGF levels have been associated with poor survival in NSCLC (40–42), to date no clear relationship between HGF expression and MET activation has been reported, making the utility of HGF as a predictive marker of response to MET inhibition difficult to determine (43).

The data from the present study indicate that exposure parameters for tepotinib in Japanese patients do not differ significantly

from those in patients of other ethnicities, further supporting the development of tepotinib in Japanese patients (33).

In summary, in Japanese patients with advanced solid tumors, tepotinib is generally well tolerated, and no DLT was observed. PK parameters in Japanese patients are comparable with those in non-Japanese patients, and first signs of antitumor activity were noted in Japanese patients, supporting further development of tepotinib in this population with the RP2D of 500 mg once daily that was confirmed in other populations.

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Conflict of interest statement

Andreas Johne is an employee of Merck Healthcare KGaA, Darmstadt, Germany. Barbara Sarholz is an employee of Merck Healthcare KGaA, Darmstadt, and a stockholder of the same company. Morihiro Watanabe is an employee of Merck Biopharma Co., Ltd., Tokyo, Japan. Kohei Shitara reports paid consulting or advisory roles for Astellas, Bristol-Myers Squibb, Lilly, MSD, Ono, Pfizer and Takeda; honoraria from AbbVie, Novartis and Yakult; and research funding from Astellas, Chugai, Daiichi Sankyo, Lilly, Medi Science, MS, Ono, Sumitomo Dainippon, and Taiho. Kentaro Yamazaki, Takahiro Tsushima, Toshihiko Doi, Tateaki Naito and Nobuaki Matsubara declare no conflict of interest.

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